Chemotherapy in Conjunction With Blood-Brain Barrier Modification in Patients With Cerebral Metastasis

ONE OF THE MAJOR PHENOMENA responsible for the failure of chemotherapy in the treatment of central nervous system (CNS) tumors may be the unique anatomic aspect of the blood-brain barrier. This structural barrier, composed of tight junctions between CNS capillary endothelial cells, serves primarily a protective regulatory function constraining diffusion across capillaries in relation to lipid solubility and molecular weight. Whereas it was formerly suggested that there was no effective barrier to drug delivery in CNS tumors, more recent studies indicate that considerable variations in barrier integrity exist between tumors, within the same tumor and particularly at the actively proliferating edge of a tumor. The clinical expression of the barrier is exemplified by the reports of increasing size of brain metastases when other extraneural parenchymal sites of tumor invasion regressed due to systemic chemotherapy.

The extent to which the blood-brain barrier limits drug delivery to CNS tumors remains an area of controversy and extensive investigation. Expansion of our studies in animals provided the basis for clinical trials, and we are presently evaluating clinical efficacy in a Phase II trial using combination chemotherapy (methotrexate sodium given intra-arterially and leucovorin calcium rescue by mouth, cyclophosphamide given intravenously and procarbazine given orally) in patients with glioblastoma, CNS metastasis and CNS lymphoma. To date, 89 patients have received combination chemotherapy in conjunction with blood-brain barrier modification in 590 procedures.

In our small pilot series of seven patients with CNS metastasis (from breast, lung or testicle), three observations are of note. In one patient, a metastatic lesion was evident on enhanced computed tomographic (CT) scan only after osmotic barrier modification, supporting the existence of a completely intact blood-brain barrier in the tumor. Second, in another patient there was radiographic documentation of tumor regression in those areas of the brain infused while tumor progressed in portions of the brain distant from the areas of barrier opening. Third, the increased delivery of chemotherapeutic agents associated with barrier modification may be of benefit even in those patients who have undergone surgical and radiation therapy and systemic chemotherapy.

We have observed the following complications in our overall series of 89 patients: infarcts (3%), transient exacerbation of preexisting neurologic deficits—presumably due to an increase in brain water secondary to blood-brain barrier modification—(50%), seizures (15%) and readmission to hospital when patients have fever and granulocytopenia (33%). The significance of these studies relates directly to the grave prognosis associated with cerebral metastasis. Drug delivery is a major factor in treatment and reversible osmotic blood-brain barrier modification is likely to enhance the delivery of cytoreductive agents with minimal toxicity.

EDWARD A. NEUWELT, MD
SUELLEN A. HILL, RN
Portland, Oregon

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Stereotactic Interstitial Irradiation (Brachytherapy) of Malignant Gliomas

BRACHYTHERAPY involves implanting radioactive sources directly into a tissue to deliver a calculated dose of radiation to a specific volume of that tissue. The technique has special appeal in neuro-oncology. The doses that have been delivered to the periphery of a brain tumor by brachytherapy are in the range of 3,000 to 12,000 rads compared with about 6,000 rads for standard teletherapy. The radiation dose delivered by combined brachytherapy and teletherapy may be substantial for the treatment of malignant gliomas.

Three factors have provided the impetus for an aggressive reevaluation of brachytherapy in managing malignant gliomas. The evolution of computed tomographic (CT) imaging technology has been combined with CT-scan-compatible stereotactic equipment and with improved computerized planning of radiation therapy. Current practice requires a confirmatory stereotactic biopsy of the lesion followed by placement of catheters into the tumor in locations selected on the basis of computer-generated isodose curves that precisely encompass the area on CT scan. The final array of the radioactive sources are afterloaded into the catheters. The sources are left in place until the calculated total dose has been delivered at a dose rate of 20 to 100 rads per hour. The dose rate depends on the specific activity of the isotope, the number of radioactive sources and their geometric distribution. The isotope ribbons and catheters are removed at the bedside on completing the radiotherapy plan.

The treated area undergoes radionecrosis and the fate of this damaged tissue is critical to the success, failure and complications of the therapy. If this technique is to be curative, the tumor under treatment must be localized and completely contained within the isodose curves that provide a dose sufficient to destroy the tumor. If these criteria are not met, then the treatment is palliative at best. In some patients, a delayed radionecrosis in the tumor volume can be progressively harmful by producing intractable cerebral edema. The experience of Gutin and Leibel with high-energy iodine 125 sources has resulted in a need for a craniotomy to remove a radionecrotic mass in about 30% of patients after implantation. Many of these patients, however, will have excellent long-term control of their disease, and the duration of survival achieved with recurrent malignant gliomas is superior to the best chemotherapeutic trials. The quality of prolonged life, however, has yet to be satisfactorily reported.

Many factors have to be studied before brachytherapy is recommended as standard therapy for malignant glioma. What role might the magnetic resonance imaging scan have in selecting focal versus diffuse gliomas? What is the best radiologic technique to define the "living" perimeter of the tumor? Should the treatment be restricted to recurrent disease or might it supplement teletherapy at some unknown ideal interval after completion of initial treatment and in relation to an unknown schedule of chemotherapy and radiosensitizers? What isotope is best? What is the ideal dose-rate and total dose